Received: 28 July 2023 | Accepted: 11 August 2023

DOI: 10.1002/psp4.13039

ARTICLE

Dosing recommendation of nirmatrelvir/ritonavir using an integrated population pharmacokinetic analysis

Phylinda L. S. Chan[1] | **Ravi Shankar P. Singh**[2] | **Donna S. Cox**[3] | **Haihong Shi**[4] | **Bharat Damle**[5] | **Timothy Nicholas**[4]

[1]Worldwide Research, Development and Medical, Pfizer R&D UK Ltd., Sandwich, Kent, UK

[2]Worldwide Research, Development and Medical, Pfizer Inc., Cambridge, Massachusetts, USA

[3]Worldwide Research, Development and Medical, Pfizer Inc., Collegeville, Pennsylvania, USA

[4]Worldwide Research, Development and Medical, Pfizer Inc., Groton, Connecticut, USA

[5]Worldwide Research, Development and Medical, Pfizer Inc., New York, New York, USA

Correspondence
Phylinda L. S. Chan, Pfizer R&D UK Ltd., Discovery Park House, Ramsgate Rd, Sandwich, Kent CT13 9NJ, UK.
Email: phylinda.chan@pfizer.com

Abstract

Protease inhibitor nirmatrelvir coadministered with ritonavir as a pharmacokinetic enhancer (PAXLOVID™; Pfizer Inc) became the first orally bioavailable antiviral agent granted Emergency Use Authorization in the United States in patients ≥12 years old with mild to moderate coronavirus disease 2019 (COVID-19). This population pharmacokinetic analysis used pooled plasma nirmatrelvir concentrations from eight completed phase I and II/III studies to characterize nirmatrelvir pharmacokinetics when coadministered with ritonavir in adults with/without COVID-19. Influence of covariates (e.g., formulation, dose, COVID-19) was examined using a stepwise forward selection ($\alpha = 0.05$) and backward elimination ($\alpha = 0.001$) approach. Simulations with 5000 subjects for each age and weight group and renal function category were performed to support dosing recommendations of nirmatrelvir/ritonavir for adults with COVID-19 and guide dose adjustments for specific patient populations (e.g., renal insufficiency, pediatrics). The final model was a two-compartment model with first-order absorption, including allometric scaling of body weight and dose-dependent absorption (power function on relative bioavailability). Nirmatrelvir clearance (CL) increased proportionally to body surface area–normalized creatinine CL (nCLCR) up to 70 ml/min/1.73 m^2 and was independent of nCLCR above the breakpoint. Significant covariates included carbamazepine or itraconazole coadministration as markers for drug interactions, COVID-19 on CL, formulation on relative bioavailability, and age on central volume of distribution. Simulation results support current dosing recommendations of nirmatrelvir/ritonavir 300/100 mg twice daily (b.i.d.) in adults with normal renal function or mild impairment and pediatrics (12 to <18 years) weighing ≥40 kg and nirmatrelvir/ritonavir 150/100 mg b.i.d. in adults with moderate renal impairment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Nirmatrelvir/ritonavir was conditionally authorized by the US Food and Drug Administration in December 2021 as the first orally bioavailable treatment for mild to moderate coronavirus disease 2019 (COVID-19). This was the first Emergency Use Authorization granted without pediatric clinical data, based solely on preliminary population pharmacokinetic analyses using data from a first-in-human study and simulation.

WHAT QUESTION DID THIS STUDY ADDRESS?

Nirmatrelvir exposures were simulated to support nirmatrelvir/ritonavir dosing recommendations for adults with COVID-19 and guide dose adjustments for specific populations (e.g., renal insufficiency, pediatric patients).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This analysis of pooled phase I/II/III study data enabled full characterization of nirmatrelvir pharmacokinetics when coadministered with ritonavir in adults with/without COVID-19. Simulations indicated doses at which most renally impaired (mild, 300 mg; moderate, 150 mg) and pediatric (12 to <18 years and ≥40 kg, 300 mg) patients would maintain nirmatrelvir concentrations at ≥90% of the effective concentration.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Findings support nirmatrelvir/ritonavir dosing recommendations, including in renally impaired and pediatric populations, and may help inform dosing in other groups.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic remains a challenge, with more than 767 million confirmed cases and more than 6.9 million COVID-19–attributable deaths as of July 2023.[1] In December 2021, nirmatrelvir, a potent and specific inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) main protease, coadministered with ritonavir as a pharmacokinetic (PK) enhancer (PAXLOVID™; Pfizer Inc) became the first orally bioavailable antiviral agent granted Emergency Use Authorization (EUA) in the United States for COVID-19 treatment.[2–4] The EUA and recent licensure were based on findings from the phase II/III Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients study (EPIC-HR; NCT04960202), which demonstrated an 88% relative risk reduction in COVID-19–associated hospitalization or death among high-risk patients with moderate COVID-19 who initiated nirmatrelvir/ritonavir treatment ≤5 days of symptom onset.[3–5] The licensure applies to adults who are at high risk of progression to severe COVID-19 disease based on demographic, lifestyle, or underlying medical characteristics; approved dosing is 300-mg nirmatrelvir with 100-mg ritonavir twice daily (b.i.d.) for 5 days.[4,6] The dosing is intended so that >90% of those treated would achieve a minimum concentration (C_{min}) ≥ 90% effective concentration (EC_{90}; i.e., the concentration at which 90% of inhibition of SARS-CoV-2 viral replication occurs[7]) of 292 ng/ml.[8,9]

In the current analysis, a preliminary population PK model (based on 20 healthy adults)[8] was updated to fully characterize nirmatrelvir PK in the presence of ritonavir, including the evaluation of potential relevant covariates (e.g., age, body weight) using data from eight completed phase I and phase II/III studies. In addition to the phase II/III EPIC-HR study,[5] these studies included a phase I first-in-human study,[8] phase I studies in adults with/without renal or hepatic impairment, and drug–drug interaction studies evaluating the effects of nirmatrelvir/ritonavir on the PK of dabigatran, midazolam, carbamazepine, and itraconazole (Table 1).[5,8,10–12] For hepatic impairment, participants were required to have stable hepatic impairment that met the criteria for Class B (7–9 points) of the Child-Pugh classification with no clinically significant change in disease status within 28 days before screening. Notably, the EPIC-HR study[5] was carried out between July and December 2021 when Omicron (B.1.1.529 and descendant lineages) was designated as a variant of concern.[13]

The objectives of this study included PK characterization of nirmatrelvir coadministered with ritonavir in healthy adult participants and adults with COVID-19,

TABLE 1 Clinical studies included in the population PK analysis.

ClinicalTrials.gov study number	Study design	*N*	Nirmatrelvir dosing regimens	Nirmatrelvir plasma PK sampling
Phase I				
NCT04756531[8]	A phase I randomized, double-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study to evaluate the safety, tolerability, and PK of nirmatrelvir in healthy adult participants	43	PART 1 SAD suspension • Cohort 1: 150 mg,[a] 1500 mg,[a] 750 mg/RTV[b] • Cohort 2: 500 mg,[a] 250 mg/RTV,[b] 250 mg/RTV (fed)[b,c] PART 2 MAD suspension • Cohort 3: 75 mg/RTV q12h • Cohort 4: 250 mg/RTV q12h • Cohorts 5 & 6: 500 mg/RTV q12h PART 3 relative bioavailability/food effect[a] • 250-mg suspension, 250-mg tablet, 250-mg tablet (fed)[c] PART 4 metabolism & excretion suspension[d] • SD 300 mg/RTV PART 5 supratherapeutic exposures suspension[b] • 750 mg/RTV at 0, 2, & 4 h	PART 1 SAD: before treatment, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 h PART 2 MAD: before treatment on Days 2, 3, 6, & 8; before dose, 0.5, 1, 1.5, 2, 4, 6, 8, &12 h after treatment on Days 1, 5, & 10; and 16, 24, & 48 h after treatment on Day 10 PART 3: before treatment, 0.5, 1, 1.5, 2, 4, 8, 12, 16, 24, & 48 h PART 4: before treatment, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 h PART 5: before treatment, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, & 96 h
NCT05005312	A phase I, nonrandomized, open-label study to assess the PK, safety, and tolerability of nirmatrelvir/RTV in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function	16	100-mg tablet • Cohort 1: normal hepatic function: SD 100 mg/RTV[d] • Cohort 2: moderate hepatic impairment: SD 100 mg/RTV[d]	Before treatment, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, & 48 h
NCT04909853[10]	A phase I, nonrandomized, open-label study to assess the PK, safety, and tolerability of nirmatrelvir/RTV in adult participants with renal impairment and in healthy participants with normal renal function	34	100-mg tablet • Cohort 1: moderate renal impairment: SD 100 mg/RTV[d] • Cohort 2: mild renal impairment: SD 100 mg/RTV[d] • Cohort 3: normal renal function: SD 100 mg/RTV[d]	Before treatment, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, & 48 h
NCT05064800[12]	A phase I, open-label, three-treatment, six-sequence, three-period crossover study to estimate the effect of nirmatrelvir/RTV and RTV on the PK of dabigatran (a P-gp substrate) in healthy participants	23	100-mg tablet • Treatment 1: SD dabigatran 75 mg[a] • Treatment 2: 300 mg/RTV q12h for 2 days (three doses total); SD dabigatran 75 mg on Day 2 • Treatment 3: RTV 100 mg q12h for 2 days (three doses total); SD dabigatran 75 mg on Day 2[a]	Predose, 1, 2, 4, 6, 8, 12, 16, 24, 36, & 48 h after treatment on Day 2 Note: Additional whole-blood PK samples were collected using a microsampling device (Tasso®, Tasso, Inc., Seattle, WA, USA) at 1, 2, 4, 6, 8, & 12 h after treatment on Day 2

(Continues)

TABLE 1 (Continued)

ClinicalTrials.gov study number	Study design	*N*	Nirmatrelvir dosing regimens	Nirmatrelvir plasma PK sampling
NCT05032950[12]	A phase I, open-label, three-treatment, six-sequence, three-period crossover study to estimate the effect of nirmatrelvir/RTV and RTV on the PK of midazolam (a CYP3A substrate) in healthy participants	11	100-mg tablet • Treatment 1: SD midazolam 2 mg[a] • Treatment 2: 300 mg/RTV q12h for 5 days (9 doses total); SD midazolam 2 mg on Day 5 • Treatment 3: RTV 100 mg q12h for 5 days (9 doses total); SD midazolam 2 mg on Day 5[a]	Predose on Days 1, 3, & 5; 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, & 72 h after treatment on Day 5 Note: Additional whole-blood PK samples were collected using a microsampling device (Tasso®) before treatment, 2, 3, 4, 8, & 12 h after treatment on Day 5
NCT04962230[11]	A phase I, open-label, fixed sequence, two-period crossover study to estimate the effect of carbamazepine (a strong CYP3A inducer) on the PK of nirmatrelvir/RTV in healthy participants	12	150-mg tablet • Period 1: SD 300 mg/RTV • Period 2: carbamazepine q12h for 15 days, titrated from 100 mg to 300 mg; SD 300 mg/RTV on Day 14	Predose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, & 48 h after treatment on Day 14
NCT04962022[11]	A phase I, open-label, fixed sequence, two-period crossover study to estimate the effect of itraconazole (a strong CYP3A inhibitor) on the PK of nirmatrelvir/RTV in healthy participants	11	Suspension • Period 1: 300 mg/RTV q12h for 3 days (5 doses total) • Period 2: itraconazole 200 mg q.d. for 8 days; 300 mg/RTV q12h on Days 4, 5, & 6 (5 doses total)	Period 1: before treatment on Days 1, 2, & 3; 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, & 48 h after treatment on Day 3 Period 2: before treatment on Days 1, 4, 5, & 6; 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, & 72 h after treatment on Day 6
Phase II/III				
NCT04960202[5]	An interventional efficacy and safety, phase II/III, double-blind, two-arm study to investigate orally administered nirmatrelvir/RTV compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness	1087 (33 in the sentinel cohort)	150-mg tablet[e] • 300 mg/RTV q12h for 5 days (10 doses total)	Day 1: one sample collected 30 to 90 min after treatment if feasible Day 5: one sample before treatment (up to 2 h before study intervention administration) if feasible; otherwise, collected anytime during the visit Note: Additional optional PK samples may be collected via home health visit, in-clinic visits, or self-collected whole-blood microsample (Tasso® device)

Abbreviations: COVID-19, coronavirus disease 2019; CYP, cytochrome P450; MAD, multiple ascending dose; *N*, number of participants included in the current population PK analysis; P-gp, P-glycoprotein; PK, pharmacokinetics; q12h, every 12 hours; q.d., once a day; RTV, ritonavir 100 mg; SAD, single ascending dose; SD, single dose.

[a]Excluded from the current population PK analysis.

[b]RTV was administered at −12, 0, and 12 h with respect to nirmatrelvir/RTV dosing.

[c]High-fat, high-calorie meal.

[d]RTV was administered at −12, 0, 12, and 24 h with respect to nirmatrelvir/RTV dosing.

[e]Nirmatrelvir 300 mg as three tablets of 100 mg for participants in the sentinel cohort.

identification of covariates impacting exposure to nirmatrelvir in the presence of ritonavir, and simulation of nirmatrelvir exposures to support dosing recommendations of nirmatrelvir/ritonavir for adults with COVID-19 and guide dose adjustments or labeling recommendations for specific populations, such as those with renal or hepatic insufficiency and pediatric (12–<18 years old and ≥40 kg) populations.

METHODS

Study designs and patient populations

This analysis included data from seven phase I studies in adult participants (serial sampling) and one phase II/III study in nonhospitalized symptomatic adults with COVID-19 who were at risk of progression to severe illness (sparse sampling).[5,8,10–12] All studies were conducted in compliance with ethical principles from the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice Guidelines, and all local regulatory requirements, including those affording greater protection to the safety of trial participants. Final protocol and related documents were reviewed and approved by investigational review boards or ethics committees for each site, and all subjects provided informed consent before study participation. Additional study details, including PK sampling, are included in Table 1. Studies varied by nirmatrelvir formulation (suspension; or 100-mg or 150-mg tablets), regimen (doses and dosing frequency), fed versus fasted state, and subject population (healthy, COVID-19, hepatically or renally impaired). Across studies, only plasma concentrations collected from nirmatrelvir/ritonavir treatment arms were included in the analysis.

Study assessments

In the first-in-human study (NCT04756531), plasma samples were analyzed for nirmatrelvir concentrations at Pfizer (Groton, CT) using validated liquid chromatography with tandem mass spectrometric detection (LC–MS/MS). For all other studies, samples were analyzed at York Bioanalytical Solutions (York, UK) using a validated LC–MS/MS method.

Plasma concentrations below the lower limit of quantitation (LLOQ) for nirmatrelvir (10 ng/ml) were reported as below the limit of quantitation (BLQ). Nirmatrelvir concentrations that were BLQ were set to 0 and treated as missing; no data imputation for these or missing nirmatrelvir concentrations was performed. Individuals for whom all nirmatrelvir concentrations were BLQ or who only had nirmatrelvir/ritonavir dosing records were retained in the population PK analysis set.

Model development

Nonlinear mixed-effects modeling (NONMEM) version 7.5.0 was used for all model estimations.[14] Perl-speaks-NONMEM version 5.2.6 was used for stepwise covariate modeling (SCM), prediction-corrected visual predictive check (pcVPC), and sampling importance resampling (SIR).[15] R version 4.1.1 was used for preprocessing and postprocessing and for summarizing and plotting results.[16] The NONMEM model is included in Data S1.

Key assumptions used in the modeling and simulations are described in Table S1. The base model was established from the preliminary population PK model described previously[8] and was a two-compartment model with first-order elimination and first-order absorption. Disposition kinetics were modeled using a parameterization involving clearance (CL), central volume of distribution (V_2), intercompartmental clearance (Q), peripheral volume of distribution (V_3), first-order absorption rate constant (k_a), and relative bioavailability (F1), with baseline body weight (BBWT) and baseline body surface area–normalized creatinine CL (nCLCR) included in the base model as structural covariates. Effect of nCLCR on CL was modeled using a linear, power, or breakpoint model. Interindividual variability (IIV) in PK parameters was assumed to be log-normally distributed and was modeled using multiplicative random effects, whereas residual random effects were described by a combined proportional and additive model in the log domain because of model instability and high variability in phase I and phase II/III studies, respectively. The vector of IIV random effects (across parameters within each individual) with a variance–covariance matrix Ω was built only if correlation of central compartment parameters (e.g., between CL and V_2) was observed (i.e., $R^2 > 0.6$).

Potential covariates tested for significance on model parameters are outlined in Table S2. Significance of these covariates was tested with SCM. Addition of an individual covariate parameter was performed at a prespecified significance level of $\alpha = 0.05$ with the likelihood ratio test (LRT; based on the NONMEM objective function value [OFV]). A stepwise backward elimination algorithm using LRT tested for significance of an individual covariate parameter when eliminated from the full model, given retention of the others, at a prespecified significance level of $\alpha = 0.001$ (i.e., change in OFV of ≥10.83 based on a χ^2 distribution with one degree of freedom).

Model adequacy was evaluated using a pcVPC,[17] with stratification by study design variables and covariates. Both η-shrinkage and ε-shrinkage were evaluated to assess

validity (20%–30%) of using empirical Bayes estimates or post hoc individual parameter estimates for model diagnosis. A thousand data sets, identical in design to the original data set, were simulated using the final model parameters except for model uncertainty. Medians and 5th and 95th percentiles of simulated concentrations were plotted versus time after dose and compared with observed concentrations. The final model used SIR[18,19] to derive standard deviation and 95% confidence intervals (CIs) for model parameters from 1000 samples and three iterations with importance ratios of 5, 2.5, and 2 (i.e., resampling sizes of 200, 400, and 500, respectively).

Nirmatrelvir exposure simulations

Once developed, the final population PK model was used to support existing dosing recommendations and develop dosing recommendations for adults with moderate renal impairment and the pediatric population at predetermined age and body weight bands (i.e., 12–<18 years old and ≥40 kg). The dosing regimen used in the phase II/III study (i.e., nirmatrelvir/ritonavir 300/100 mg b.i.d. for 5 days) and an alternative dosing regimen of 150/100 mg b.i.d. were used for these simulations. Ritonavir dosage was selected based on approved labels for other protease inhibitors coadministered with ritonavir as a PK enhancer for the treatment of HIV infection, and no other ritonavir dosages were tested.[4,8] Simulations using a sample size of 5000 were performed separately for each age (adult and 12–<18 years old) or weight group and renal function category (normal, nCLCR ≥90 ml/min/1.73 m^2; mild impairment, nCLCR 60–<90 ml/min/1.73 m^2; moderate impairment, nCLCR 30–<60 ml/min/1.73 m^2). For adults with normal renal function, covariates were sampled from a multivariate normal density based on the covariance of age, weight, and nCLCR observed in the population PK data in the phase II/III study. For renal impairment simulations, covariate nCLCR was sampled from a uniform distribution with the interval set to the cutoff values for the specific renal function categories. For pediatric subjects (12–<18 years old), body weight was sampled using US Centers for Disease Control and Prevention pediatric growth charts,[20] and nCLCR was set to 100 ml/min/1.73 m^2 to simulate normal renal function. Nirmatrelvir concentration profiles were simulated using parameter estimates from the final population PK model incorporating IIV but not residual errors or model uncertainty. Dose recommendations were based on nirmatrelvir exposures matching adults with COVID-19 and normal renal function following nirmatrelvir/ritonavir 300/100 mg b.i.d. given orally for 5 days, and >90% of simulated subjects achieving $C_{min} \geq EC_{90}$ of 292 ng/ml.[7–9]

RESULTS

Observed data

The analysis data set included 1237 participants; 87.9% were from the phase II/III study (Table 1). The 5149 plasma nirmatrelvir samples collected included 4404 evaluable samples from 1161 participants within the phase I and phase II/III studies and 745 BLQ samples (14.5%) from 485 participants; within the phase II/III study, 73 participants had exclusively BLQ samples. Notably, when excluding BLQ samples, 265 participants had only one evaluable observation. Demographics of all participants included in the population PK analysis set are described in Table 2. Most participants were White and had normal renal function and COVID-19.

Figure 1 shows the observed dose-normalized (300 mg) plasma nirmatrelvir concentrations over time after dose for different populations and treatments stratified by formulation and renal function. Nirmatrelvir concentrations appeared to be lower and higher when coadministered with carbamazepine and itraconazole, respectively (Figure 1a). Overall, nirmatrelvir concentrations were more variable among adults with COVID-19 (phase II/III study) than in healthy participants. Nirmatrelvir concentrations among adults with COVID-19 appeared comparable across formulations, which included 100-mg tablets administered to a sentinel cohort of 33 participants and 150-mg tablets administered to the rest of the study population. Among adults with normal renal function who were given 150-mg tablets, concentrations were lower among healthy adults than in those who had COVID-19 (Figure 1b), likely reflecting that the former received a single dose while the latter were dosed twice a day.

Population PK modeling

Using all phase I and phase II/III data, the initial base population PK model was a two-compartment model that included first-order absorption; IIV in CL, V_2, k_a, and V_3; standard allometric scaling of BBWT with fixed exponents of 0.75 for CLs and 1 for volumes to reduce collinearity among covariates; and additive and proportional errors on the log scale. Additive error was fixed to 0.0001 ng/ml during model development as a result of model instability. The model was then modified with the use of a power model for the nCLCR effect on CL, normalized to the estimated breakpoint, below the estimated breakpoint of 70 ml/min/1.73 m^2 and a power function for dose effect on F1 (Data S1), normalized to 300 mg, based on substantial reductions in OFV observed in association with these modifications. Additionally, a

TABLE 2 Demographics of participants in the population pharmacokinetic analysis data set overall and by population.

	All	COVID-19	Healthy
Participants, *n* (%)[a]	1237	1087 (87.9)	150 (12.1)
Plasma samples, *n* (%)[a]	5149	2488 (48.3)	2661 (51.7)
Sex, *n* (%)[a]			
Male	657 (53.1)	546 (44.1)	111 (9.0)
Female	580 (46.9)	541 (43.7)	39 (3.2)
Race, *n* (%)[a]			
White	865 (69.9)	777 (62.8)	88 (7.1)
Black/African American	105 (8.5)	56 (4.5)	49 (4.0)
Asian	162 (13.1)	152 (12.3)	10 (0.8)
American Indian/Alaska Native	95 (7.7)	95 (7.7)	0
Other	4 (0.3)	1 (<0.1)	3 (0.2)
Unknown	6 (0.5)	6 (0.5)	0
Body weight, kg			
Median	79.4	79.8	77.3
Range	42.0–158	42.0–158	52.7–114
Age, y			
Median	45.0	45.0	49.0
Range	18.0–86.0	18.0–86.0	20.0–76.0
Baseline CL_{cr}, ml/min			
Median	128	133	103
Range	19.5–421	20.7–421	19.5–277
Baseline nCLCR, ml/min/1.73 m^2			
Median	119	124	95.8
Range	15.8–318	22.8–318	15.8–247
Baseline body mass index, kg/m^2			
Median	27.9	28.2	26.5
Range	16.6–58.1	16.6–58.1	19.7–40.3
Renal function, *n* (%)[a]			
Normal (nCLCR ≥90 ml/min/1.73 m^2)	1045 (84.5)	936 (75.7)	109 (8.8)
Mild (60 ≤ nCLCR <90 ml/min/1.73 m^2)	147 (11.9)	122 (9.9)	25 (2.0)
Moderate (30 ≤ nCLCR <60 ml/min/1.73 m^2)	35 (2.8)	27 (2.2)	8 (0.6)
Severe (nCLCR <30 ml/min/1.73 m^2)	10 (0.8)	2 (0.1)	8 (0.6)

Abbreviations: CL_{cr}, creatinine clearance; COVID-19, coronavirus disease 2019; nCLCR, body surface area–normalized creatinine clearance.

[a]Percentages given reflect percentages of the total number of participants rather than within each group.

separate proportional error was added to account for high variability in the phase II/III study (approximately two- to threefold higher than for phase I data), further decreasing OFV.

Using SCM, selected covariates resulting in a large decrease in OFV and increase in IIV (>47% for k_a, and ~4%–5% for CL and V_3) included concomitant medications, age, obesity status (i.e., baseline body mass index [BBMI] ≥30 kg/m^2), and race on CL; formulation on F1; age, BBMI, COVID-19, and sex on V_2; and dose effect on k_a. IIV increased when few covariates were included in the SCM, suggesting complex interactions between some covariates. SCM was then repeated manually for each of these covariates subject to the additional requirement of ≥2% reduction in IIV for any of the PK parameters; the first covariate selected by SCM, concomitant medications

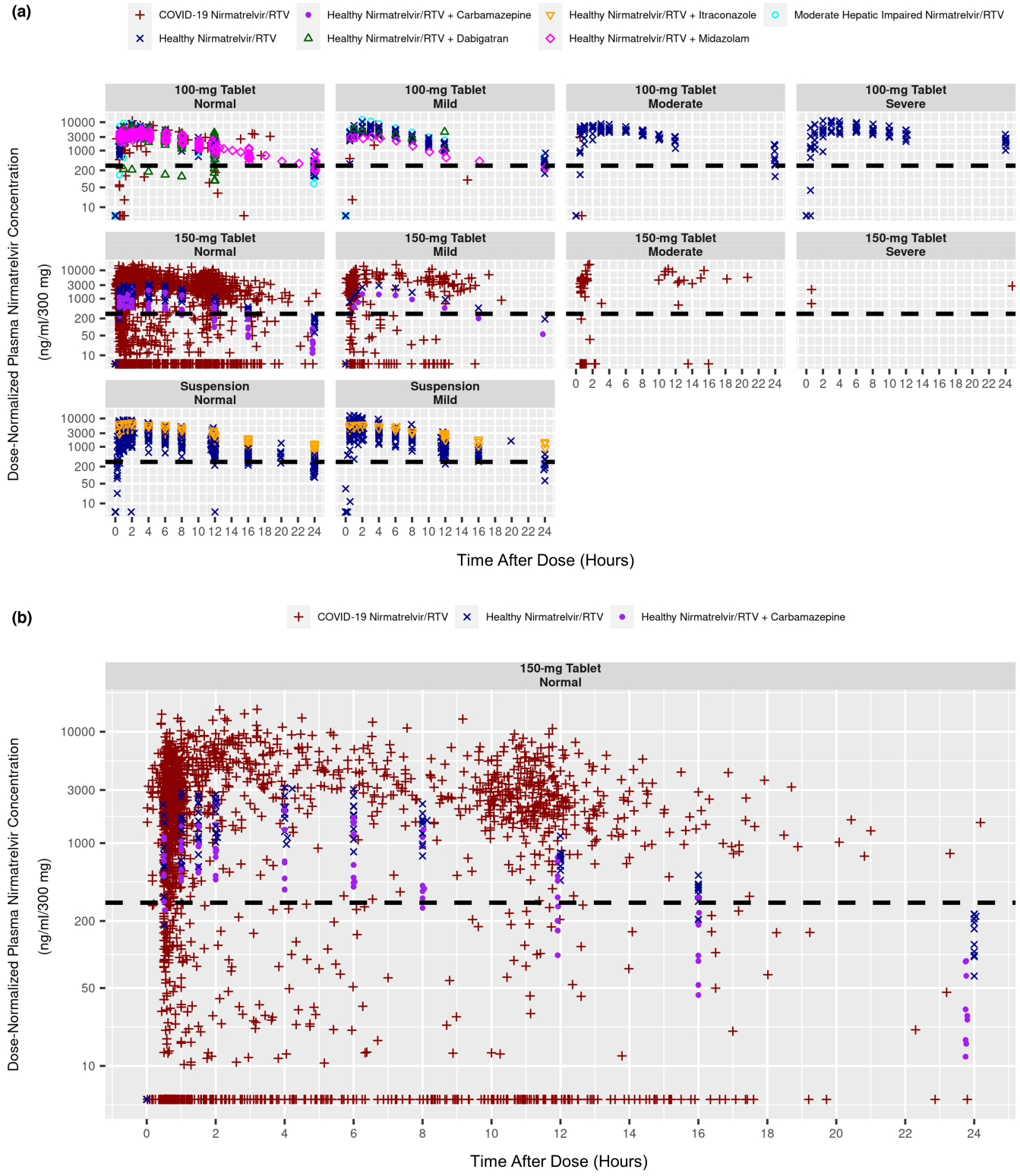

FIGURE 1 Observed dose-normalized plasma nirmatrelvir concentration versus time after dose (a) by formulation and renal function category and (b) with the 150-mg tablet in individuals with normal renal function. Symbols represent individual observations. The dashed horizontal line represents the target exposure in vitro EC_{90} of 292 ng/ml. BLQ samples are shown below the LLOQ of 10 ng/ml. BLQ, below the limit of quantitation; EC_{90}, 90% effective concentration; LLOQ, lower limit of quantitation; RTV, ritonavir 100 mg.

on CL, was selected as the starting model. Covariates of COVID-19 and hepatic impairment on CL were evaluated at this stage out of interest, despite not being selected by SCM. Using this approach, the final covariate model included carbamazepine, itraconazole, and COVID-19 on CL; age on V_2; and formulation on F1. The elimination of

any of these covariates resulted in an OFV increase of ~20 or more units.

Thus, the final model was a two-compartment model ($V_2 = 56.9$ L; $V_3 = 12.8$ L at 300 mg) with first-order elimination (CL = 9.09 L/h at 300 mg); first-order absorption ($k_a = 0.873$/h); a BBWT effect (normalized to 70 kg) on CLs and volumes modeled by a power function and fixed exponents (0.75 for CL and Q; 1 for V_2 and V_3); a nCLCR effect on CL modeled by a power function for nCLCR (normalized to the estimated breakpoint 70 ml/min/1.73 m^2) below the estimated breakpoint (1.05); a dose effect on F1 (normalized to 300 mg) modeled by a power function (−0.409); an age effect on V_2 (normalized to 45 years) modeled by a power function (−0.425); two separate fractional concomitant medication effect parameters for carbamazepine (0.740) and itraconazole (−0.308) on CL; a fractional formulation effect (150-mg tablet) on F1 (−0.379); a fractional COVID-19 effect on CL (−0.341); IIV on CL (35.9% coefficient of variation [CV]), V_2 (27.3% CV), k_a (60.7% CV), and V_3 (58.7% CV) across all participants; two separate proportional residual error parameters for phase I (32.4%) and phase II/III (139%) data; and an additive error fixed to 10 ng/ml (Table 3). In general, fixed-effects and random-effects parameters were well estimated with percentage relative standard error (%RSE) <30%, other than IIV for CL (%RSE = 48.8%). All η-shrinkage were >30% as a result of the majority of data being sourced from the phase II/III outpatient study, where a sparse sampling approach was implemented. Although the inclusion of variance–covariance matrix Ω reduced OFV, it was not included because all correlations were <0.6. Table 3 also shows the mean, %RSE, median, and 2.5th and 97.5th percentiles for each parameter generated from SIR. Of note, population estimates for V_3 and IIV in V_2 were just outside the 95% CIs generated using SIR. Observed data stratified by study and data simulated using the final model were in good agreement (Figure 2). Similar to concentration-time profiles (Figure 1), pcVPC prediction intervals (Figure 2) showed high variability in the phase II/III study compared with phase I study data.

Nirmatrelvir exposure simulations

Tables 4 and S3 show predicted Day 5 nirmatrelvir exposure parameters, percentages of simulated subjects achieving $C_{min} \geq EC_{90}$ on Day 1 and Day 5, and the ratio of median C_{min} to that of adults with normal renal function for simulated adults with/without impaired renal function and pediatric subjects. Figure 3 shows the distribution of predicted Day 5 nirmatrelvir C_{min} in simulated subjects by dosing regimen and renal function (adults with/without renal impairment) or age and body weight group (pediatric subjects with normal renal function).

Among adults with normal renal function receiving nirmatrelvir 300 mg with ritonavir, >90% were projected to have $C_{min} \geq EC_{90}$ after the first dose. Observations were similar for adults with mild and moderate renal impairment with proposed nirmatrelvir doses of 300 mg and 150 mg, respectively, with ratios of median C_{min} to that of normal renal function of ≤1.3.

For pediatric subjects (12–<18 years old) with COVID-19 and normal renal function, all doses evaluated were projected to result in $C_{min} \geq EC_{90}$ in >90% of subjects after the first dose. However, the ratio of the median C_{min} to that of adults with normal renal function varied by weight group. Among individuals weighing ≥40 kg, the ratio was <1 on Day 1 for nirmatrelvir/ritonavir 150/100 mg and was 1.54 for 300/100 mg on Day 5.

DISCUSSION

In this population PK analysis, nirmatrelvir concentration-time data among adults with/without COVID-19 were adequately described by the presented two-compartment disposition model with first-order absorption, allometric scaling of body weight, and dose-dependent absorption described by a power function for F1, normalized to 300 mg. CL was similar to the phase I first-in-human study (9.09 vs. 8.2 L/h at 300 mg), whereas volume of distribution and k_a in the current pooled analysis were comparatively lower (70 vs. 111 L and 0.873 vs. 1.11/h, respectively); notably, subjects in the preliminary study ($n = 20$) were slightly younger (median age 34.5 years).[8] Nirmatrelvir CL decreased in cases of renal insufficiency (i.e., <70 ml/min/1.73 m^2), reflecting the primary role of renal excretion in nirmatrelvir elimination when cytochrome P450 (CYP) 3A4–mediated metabolism is inhibited by ritonavir.[7,8]

Significant covariates identified during model development included carbamazepine or itraconazole coadministration or COVID-19 on CL, formulation on F1, and age on V_2. For carbamazepine and itraconazole, estimated effects on CL (0.740 and −0.308, respectively) were in agreement with ratios of adjusted geometric means for nirmatrelvir exposure in individual studies.[11] Regarding formulation, data from the phase II/III study in adults with COVID-19 appeared consistent between 100- and 150-mg nirmatrelvir tablets. Notably, a separate phase I study (NCT05263895) was conducted to evaluate the relative bioequivalence of these nirmatrelvir formulations. Because the 150-mg tablet formulation was only evaluated among healthy participants in a single study that used a single dose, it is likely that counteracting effects of formulation on F1 and COVID-19 on CL reflect

TABLE 3 Parameter estimates for the final population pharmacokinetic model.

	Final model			SIR[a] run statistics				
Parameter	**Estimate**	**%RSE**	**Shrinkage, %**	**Mean**	**%RSE**	**Median**	**Lower 2.5th percentile**	**Upper 97.5th percentile**
CL, L/h	9.09	3.64	–	8.98	2.53	8.98	8.53	9.42
V_2, L	56.9	4.32	–	57.5	3.96	57.5	53.6	62.6
Q, L/h	1.28	14.2	–	1.02	16.9	1.02	0.704	1.36
V_3, L	12.8	11.1	–	10.2	11.2	10.1	8.22	12.7
k_a, 1/h	0.873	8.94	–	0.906	6.76	0.908	0.791	1.03
$nCLCR_{breakpoint}$, ml/min/1.73 m^2	70.1	0.03	–	70.1	0.0362	70.1	70	70.1
$nCLCR_{power} < nCLCR_{breakpoint}$	1.05	8.44	–	0.908	9.2	0.907	0.748	1.09
$F1_{power}$	−0.409	8.7	–	−0.401	7.38	−0.401	−0.458	−0.341
Effect of carbamazepine on CL	0.740	27.1	–	0.748	12.4	0.74	0.583	0.939
Effect of itraconazole on CL	−0.308	7.19	–	−0.303	5.33	−0.303	−0.332	−0.272
Effect of 150-mg tablet on F1	−0.379	10.1	–	−0.391	7.75	−0.391	−0.454	−0.331
Power of age effect on V_2	−0.425	17.6	–	−0.419	17	−0.416	−0.553	−0.285
Effect of COVID-19 on CL	−0.341	10.7	–	−0.349	9.16	−0.348	−0.41	−0.288
Proportional error phase I, %	32.4	5.69	6.28	31.9	2.12	31.9	30.7	33.4
Proportional error phase II/III,[b] %	139	3.81	–	136	2.29	136	131	142
IIV_{CL}, %CV	35.9	48.8	55.9	36.1	18.7	35.7	30.5	42.9
IIV_{V2}, %CV	27.3	17.6	68.8	31.2	10.4	31.2	27.5	34.1
IIV_{ka}, %CV	60.7	20.9	63.1	60.6	14.1	60.5	51.7	68.6
IIV_{V3}, %CV	58.7	26.6	79.2	59.3	21.4	59.2	44.9	71.6

Note: Fixed parameters: F1 = 1, normalized to 300 mg; additive error = 10 ng/ml.

Abbreviations: CL, clearance; COVID-19, coronavirus disease 2019; CV, coefficient of variation (computed as $\sqrt{\omega^2} \times 100\%$); F1, relative bioavailability; $F1_{power}$, exponent of power function for dose effect on F1 with F1 fixed to 1 and dose normalized to 300 mg; IIV, interindividual variability; k_a, first-order absorption rate constant; Q, intercompartmental clearance; nCLCR, body surface area–normalized creatinine clearance; %RSE, percent relative standard error; SIR, sampling importance resampling; V_2, central volume of distribution; V_3, peripheral volume of distribution.

[a]With three iterations with resampling size of 200, 400, and 500.

[b]ε shrinkage same as phase I proportional error.

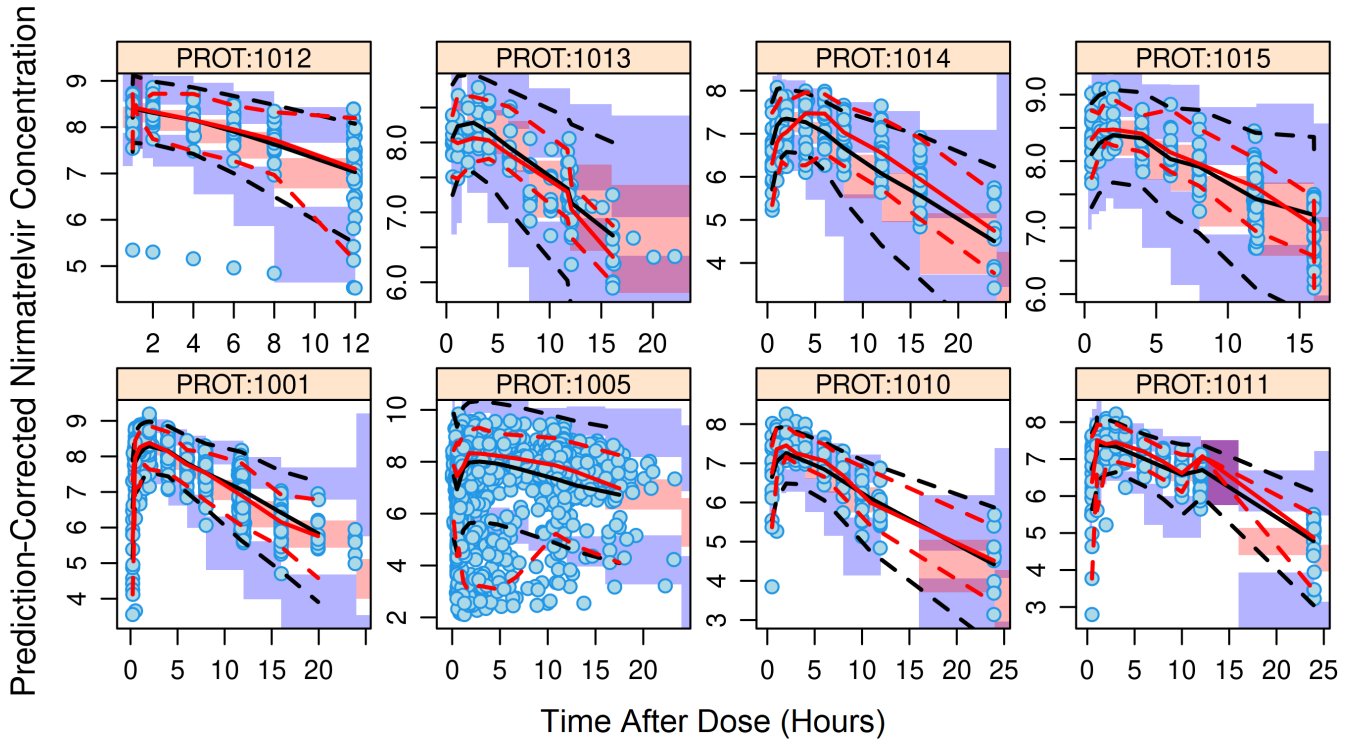

FIGURE 2 The pcVPC for the final population PK model stratified by study. Symbols represent observed nirmatrelvir concentrations. Red lines indicate median (solid line) and 5th and 95th CIs (dashed lines) of the observed data. Black lines indicate median (solid line) and 5th and 95th CIs (dashed lines) from 1000 simulations with surrounding 95% shaded area in pink and blue. CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; PROT, protocol.

TABLE 4 Predicted Day 5 C_{min} and percentage of simulated subjects with COVID-19 in various groups achieving a C_{min} value greater than or equal to the in vitro EC_{90} of 292 ng/ml following b.i.d. dosing of nirmatrelvir/ritonavir for 5 days.[a]

Group	Dose, mg[b]	Dose number	C_{min} (ng/ml)			Ratio of median to normal	% Subjects achieving $C_{min} \geq EC_{90}$
			Median	10th percentile	90th percentile		
Adults ≥40 kg with normal renal function	300	1st (Day 1)	827	445	1313	–	96.7
		10th (Day 5)	1417	593	2731	–	98
Adults with renal impairment[c]							
Mild	300	1st (Day 1)	850	467	1345	1.03	97.2
		10th (Day 5)	1478	639	2862	1.04	98.4
Moderate	150	1st (Day 1)	803	515	1220	0.97	99
		10th (Day 5)	1839	880	3466	1.3	99.7
Pediatric subjects (12 to <18 years)							
≥40 kg	300	1st (Day 1)	1093	680	1574	1.32	99.6
		10th (Day 5)	2177	1044	3889	1.54	99.8
	150	1st (Day 1)	725	452	1045	0.877	98
		10th (Day 5)	1445	693	2581	1.02	99.3

Abbreviations: b.i.d., twice daily; C_{min}, minimum concentration; COVID-19, coronavirus disease 2019; EC_{90}, 90% effective concentration; nCLCR, baseline body surface area–normalized creatinine clearance.

[a]Based on 5000 simulated subjects per group.

[b]Nirmatrelvir 150-mg tablet b.i.d. administered with ritonavir 100 mg for 5 days.

[c]Normal = nCLCR ≥90 ml/min/1.73 m^2; mild = 60 ≤ nCLCR <90 ml/min/1.73 m^2; moderate = 30 ≤ nCLCR <60 ml/min/1.73 m^2.

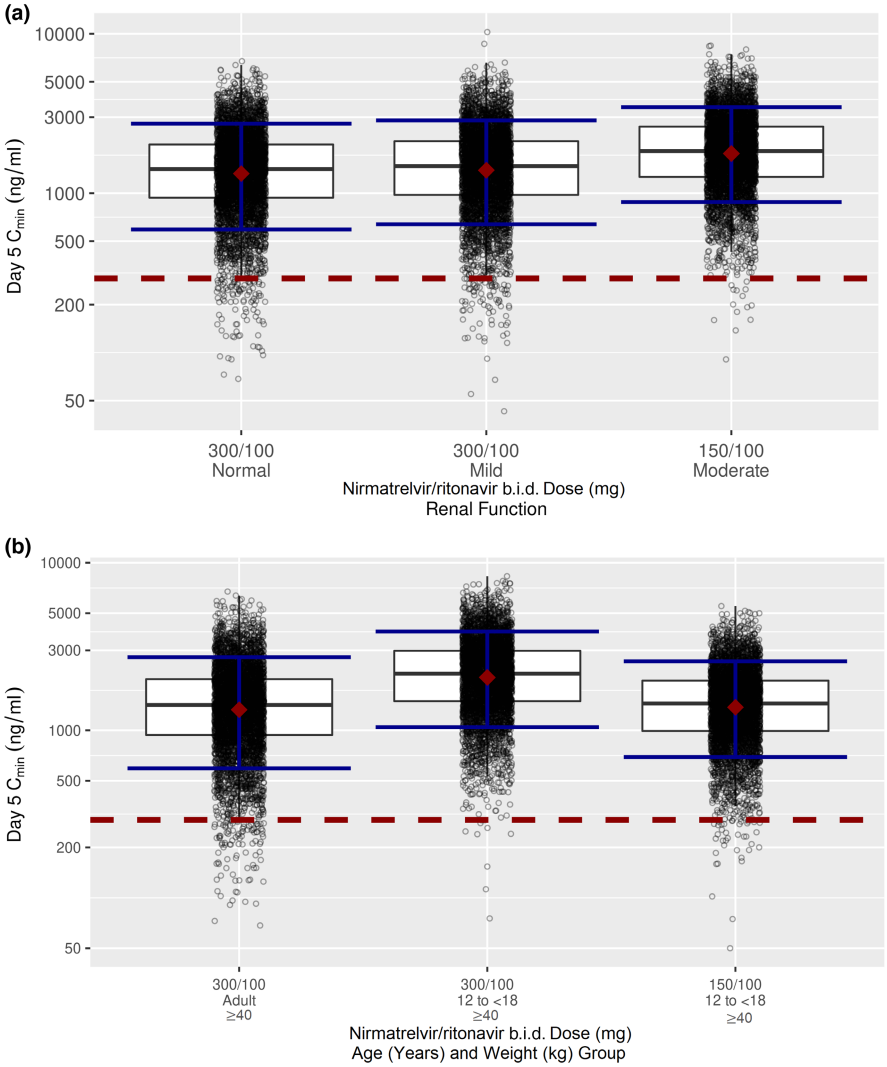

FIGURE 3 Predicted Day 5 plasma nirmatrelvir C_{min} simulated (a) in adults with COVID-19 by dosing regimen and renal function and (b) in pediatric subjects with COVID-19 by dosing regimen, age, and weight group. Symbols indicate individual predictions. Boxes indicate the interquartile range with the median of the individual group shown by a horizontal black line. Red dots represent the group means. Whisker lines represent 1.5 times the interquartile range below the first quartile or above the third quartile. The red dashed horizontal line represents the target exposure in vitro EC_{90} of 292 ng/ml. b.i.d., twice daily; C_{min}, minimum concentration; EC_{90}, 90% effective concentration.

confounding covariates; this was supported by a sudden large drop in OFV when the latter was introduced in the presence of the former. The ~25% decrease in V_2 for participants ≥80 years old was not considered clinically significant. For nirmatrelvir/ritonavir, there is a significant safety margin where the highest observed nirmatrelvir concentration was 26,400 ng/ml following an oral dose of nirmatrelvir/ritonavir 2250 mg/100 mg (nirmatrelvir split as three doses of 750 mg at 0, 2, and 4 h).[8] Geometric mean maximum concentration (C_{max}) was 15,940 ng/ml from 10 adult participants, and no serious or severe adverse effect or deaths were reported. In adults with COVID-19 in the EPIC-HR study, the highest observed nirmatrelvir concentration was 16,100 ng/ml in a participant with baseline nCLCR of ~50 ml/min/1.73 m^2.[5] No deaths were reported in the nirmatrelvir/ritonavir treatment arm. It is considered that all proposed doses for adult and pediatric populations are safe given the 90th percentiles of predicted C_{max} were <10,000 ng/ml.[5,8]

Although variability in the phase II/III study was expected to be higher than in the phase I studies because of the sparse sampling approach and outpatient setting, the approximate fourfold higher residual error for the phase II/III data was surprising. Of note, there were a high number of BLQ samples during the sparse PK sampling time windows in the phase II/III study, in addition to 73 participants who did not have any evaluable samples. Possible explanations for BLQ samples may include the physicochemical properties, effect of food, and compliance. BLQ samples collected during the planned Day 1 visit between 0.5 and 1.5 h could have possibly been attributed to differences in formulation or reduced absorption of nirmatrelvir because of permitted administration of nirmatrelvir/ritonavir with food. Conversely, several possible reasons, including compliance issues, concomitant drugs, sample labeling error, sample collection error, or some other operational challenge, may have contributed to BLQ samples on Day 5.

Based on the available data from phase I studies, BLQ samples were not expected in the phase II/III study if full compliance with the PK sampling time was followed. Given the unexpected high number of BLQ values and the

sparse sampling approach in the phase II/III study, it was not possible to estimate the likelihood of the BLQ samples. Therefore, all BLQ samples were excluded from the population PK analysis. Nevertheless, the PK parameters were well estimated in the final model with %RSE <30% for all fixed-effects and random-effects parameters, other than IIV for CL (%RSE = 48.8%). High variability in the observed nirmatrelvir data in the phase II/III study did not have any impact on capturing the central tendency and model parameter estimation.

Preliminary population PK analysis for nirmatrelvir following oral administration in combination with ritonavir was previously performed using data from the phase I first-in-human study in healthy adults (NCT04756531).[8] Results indicated that PK of nirmatrelvir administered was adequately characterized by a two-compartment disposition model with first-order absorption. Using this model to simulate nirmatrelvir/ritonavir 300-/100-mg b.i.d. dosing among a sample size commensurate with phase II/III studies demonstrated that >90% of subjects would achieve the PK/pharmacodynamic target; a nirmatrelvir dose of 300 mg with ritonavir 100 mg administered b.i.d. orally is projected to have >90% of simulated subjects achieving $C_{min} \geq EC_{90}$ of 292 ng/ml on Day 5.[7–9] Simulation using this preliminary population PK model supported the EUA in adolescents in the United States without pediatric clinical data.[3]

This study adds to the preliminary population PK model[8] by fully characterizing the PK of nirmatrelvir in the presence of ritonavir and evaluating potentially relevant covariates using data from eight completed phase I and phase II/III studies. Nirmatrelvir exposure simulations based on the population PK model were important for supporting dosing recommendations for adults with COVID-19 and to guide dose adjustments for specific patient populations (i.e., those with renal insufficiency, pediatric patients). Despite differences in models, simulations among adults with normal renal function and COVID-19 using nirmatrelvir 300 mg coadministered with ritonavir were similar to those from the preliminary model, with 96.7% and 98.0% of simulated subjects in the current analysis predicted to achieve $C_{min} \geq EC_{90}$ on Days 1 and 5, respectively, versus 90.7% and 95.7% in the preliminary analysis.[8] For adults with mild or moderate renal impairment, simulations indicated that nirmatrelvir doses of 300 and 150 mg, respectively, coadministered with ritonavir are appropriate, as indicated by >90% of simulated subjects achieving $C_{min} \geq EC_{90}$ on both Days 1 and 5, and overlap in exposures (area under the concentration-time curve [AUC], C_{max}, and C_{min}) compared with adults with normal renal function receiving a nirmatrelvir dose of 300 mg b.i.d. coadministered with ritonavir. Similarly, for pediatric subjects, simulations suggested that 300-mg nirmatrelvir doses were suitable for those 12–<18 years old weighing ≥40 kg, with >90% of simulated subjects achieving $C_{min} \geq EC_{90}$ after the first dose. This dose is being used in an ongoing phase II/III open-label study evaluating safety, PK, and efficacy of nirmatrelvir/ritonavir treatment in nonhospitalized, symptomatic pediatric participants with COVID-19 who are at increased risk of progression to severe disease (NCT05261139)[21]; findings from this study will be used for confirmatory PK modeling and simulation. Dosing recommendations for adults with severe renal impairment could not be made because of limited information.

Strengths of the analysis include the usage of data from a variety of studies, enabling the evaluation of many different potential parameters, such as the influence of formulation and population on PK for decision making in an accelerated drug development program. Population PK modeling is a powerful tool that enables the integration of sparse data from the target patient population with rich data from the healthy population. Conversely, a large majority of individuals included were from the phase II/III study, which itself was likely subject to PK inaccuracies derived from the study design. The high proportion of participants with sparse sampled data is the main reason high η-shrinkage was observed in the PK parameters. Additionally, both model development and subsequent simulations relied on several assumptions as detailed in Table S1.

Overall, this analysis of pooled phase I/II/III study data enabled development of a population PK model characterizing exposure to nirmatrelvir in the presence of ritonavir, including the identification of important covariates affecting nirmatrelvir exposure. The EPIC-HR study showed 89% lower risk of disease progression and 10-fold reduction in viral load relative to placebo when the nirmatrelvir/ritonavir dose proposed based on population PK modeling was administered ≤3 days of symptom onset.[5] Simulations were used to support dosing recommendations in special populations, including adults with renal impairment or pediatric subjects, based on >90% of simulated subjects maintaining nirmatrelvir $C_{min} \geq EC_{90}$ and comparisons to exposure (AUC, C_{max}, and C_{min}) in adults with normal renal function. These findings will help inform the effective use of nirmatrelvir/ritonavir antiviral treatment in the post–COVID-19 era.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript and performed the research. P.L.S.C., R.S.P.S., D.S.C., B.D., and T.N. designed the research. P.L.S.C., D.S.C., H.S., and T.N. analyzed the data.

ACKNOWLEDGMENTS

This study was sponsored by Pfizer Inc. Editorial/medical writing support was provided by Judith Kandel, PhD, of ICON (Blue Bell, PA) and was funded by Pfizer Inc.

FUNDING INFORMATION

This work was funded by Pfizer Inc.

CONFLICT OF INTEREST STATEMENT

All authors are employees of Pfizer and may hold stock or stock options.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. 2023. Accessed July 11, 2023. https://covid19.who.int/
2. US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. 2021. Accessed September 7, 2023. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
3. Cavazzoni P. RE: Emergency Use Authorization 105. 2023. Accessed September 7, 2023. https://www.fda.gov/media/155049/download
4. Paxlovid (nirmatrelvir/ritonavir). *Full Prescribing Information*. Pfizer Inc; 2023.
5. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386:1397-1408. doi:10.1056/NEJMoa2118542
6. US Centers for Disease Control and Prevention. People with certain medical conditions. 2022. Accessed February 28, 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
7. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science*. 2021;374:1586-1593. doi:10.1126/science.abl4784
8. Singh RSP, Toussi SS, Hackman F, et al. Innovative randomized phase I study and dosing regimen selection to accelerate and inform pivotal COVID-19 trial of nirmatrelvir. *Clin Pharmacol Ther*. 2022;112:101-111. doi:10.1002/cpt.2603
9. Eng H, Dantonio AL, Kadar EP, et al. Disposition of nirmatrelvir, an orally bioavailable inhibitor of SARS-CoV-2 3C-like protease, across animals and humans. *Drug Metab Dispos*. 2022;50:576-590. doi:10.1124/dmd.121.000801
10. Toussi SS, Neutel JM, Navarro J, et al. Pharmacokinetics of oral nirmatrelvir/ritonavir, a protease inhibitor for treatment of COVID-19, in subjects with renal impairment. *Clin Pharmacol Ther*. 2022;112:892-900. doi:10.1002/cpt.2688
11. Cox DS, Van Eyck L, Pawlak S, et al. Effects of itraconazole and carbamazepine on the pharmacokinetics of nirmatrelvir/ritonavir in healthy adults. *Br J Clin Pharmacol*. 2023;89:2867-2876. doi:10.1111/bcp.15788
12. Cox DS, Rehman M, Khan T, et al. Effects of nirmatrelvir/ritonavir on midazolam and dabigatran pharmacokinetics in healthy participants. *Br J Clin Pharmacol*. 2023:[Epub ahead of print]. doi:10.1111/bcp.15835
13. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2023. Accessed May 15, 2023. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html
14. Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ. NONMEM 7.5 Users Guides. (1989–2020). ICON plc. 2021 Accessed June 23, 2023. https://nonmem.iconplc.com/#/nonmem750
15. Perl-speaks-NONMEM (PsN) 5.2.6. (2021) 2023. Accessed June 23, 2023. https://uupharmacometrics.github.io/PsN/index.html.
16. R Core Team. *R: a language and environment for statistical computing*. R Foundation for Statistical Computing; 2023. Accessed September 7, 2023. https://cran.r-project.org/bin/windows/base/old/4.1.1/
17. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*. 2011;13:143-151. doi:10.1208/s12248-011-9255-z
18. Dosne AG, Bergstrand M, Harling K, Karlsson MO. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. *J Pharmacokinet Pharmacodyn*. 2016;43:583-596. doi:10.1007/s10928-016-9487-8
19. Dosne AG, Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. *J Pharmacokinet Pharmacodyn*. 2017;44:509-520. doi:10.1007/s10928-017-9542-0
20. Centers for Disease Control and Prevention. Clinical growth charts. 2022. Accessed September 7, 2023. https://www.cdc.gov/growthcharts/clinical_charts.htm
21. ClinicalTrials.gov. EPIC-Peds: A study to learn about the study medicine called PF-07321332 (nirmatrelvir)/ritonavir in patients under 18 years of age with COVID-19 that are not hospitalized but are at risk for severe disease. 2022. Accessed September 7, 2023. https://clinicaltrials.gov/ct2/show/NCT05261139

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chan PLS, Singh RSP, Cox DS, Shi H, Damle B, Nicholas T. Dosing recommendation of nirmatrelvir/ritonavir using an integrated population pharmacokinetic analysis. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:1897-1910. doi:10.1002/psp4.13039